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Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/800,622
Filing Date: March 16, 2004
Appellant(s): LIN ET AL.

Richard E. Fichte
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 2/23/2010 appealing from the Office action mailed 10/02/2009.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 1-16, 18-20 and 72 are pending.

Claims 1-16, 18-20 and 72 are rejected.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the

subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

EP376331	Tsuru et al.	07-1990
WO0015194	Lee et al.	03-2000
5603945	Isobe et al.	02-1997

Makoto et al. "Effect of sodium bicarbonate amount o in vitro indomethacin release from self-setting carbonated apatite cement", Pharmaceutical Research, Vol. 14, No. 4, 1997.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The Examiner notes an inadvertent error in the non-final Office Action dated 10/2/2009. The error included claim 13 in the first obviousness rejection, however, the claim depends from claim 12 which is rejected in the second obviousness rejection.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

1. Claims 1-11, 14-15, 18-20 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsuru et al. EP 376331 (Tsuru) in view of Lee et al WO 0015194 (Lee) and further in view of Isobe et al. US 5603945 (Isobe).

Tsuru teaches a slow release drug delivery granules comprising porous granules of a calcium phosphate compound having a ratio of Ca to P of 1.3 to 1.8, a porosity of 0.1 to 70%, a specific surface area of 0.1 to 50 m^2/g and a pore size of 1nm to 10 microns, fired at a temperature of 200 to 1400°C, and a drug component impregnated in pores of the granules, and a process for producing the same. The drug delivery granules of the invention has a controllable and good prolonged effect of the drug release and can be advantageously utilized in the field of a chemotherapy (abstract). The granule size can be of 5 to 500 microns, and most preferably a granule size of 10 to 100 microns (page 3, lines 46+); this disclosure reads on the sized recited on instant claims 1, 3 and 4. Tsuru discloses that the Ca/P ratio of 1.3 to 1.8. A ca/P ratio of 1.35 to 1.75 is preferable and a Ca/P ratio of 1.4 to 1.7 is more preferable (page 3, lines 15-16). Further, the porous granules have a specific surface area of 0.1 to 50 m^2/g, preferably 1 to 40 m^2/g, more preferably 10 to 30 m^2/g (page 3, lines 35+). A drug or medicine is contained in pores of the granules (page 2, line 51). The drugs contained in the pores include antibiotics (page 4, line 57). Example 6 teaches hydroxyapatite powder having a Ca/P ratio of 1.67 mixed with spherical acryl beads having an average size of 50 micron which serve as cores of granules in a stirrer and stirred under spraying of distilled water at a high speed of 5000rpm. The thus coated beads were fired at a temperature of 900 DEG C to obtain the hollow granules of hydroxyapatite

having an average granule size of 90 microns. These hollow granules have a porosity of 50%, average pore size of 200nm and specific surface area of $14.5m^2/g$. The granules are impregnated in the ADR solution to obtain drug contained in the pores with the acryl polymer beads (example 6).

Regarding the amount of polymer and/or the amount of drug loaded, since Tsuru teaches that the drug and polymers are entrapped in the pores of the apatite and since the size of the pores are the same then the amount of entrapped substance in the pores is obviously the same and the amount of drug loading should be within the capabilities of a person of ordinary skill in the art.

Tsuru did not disclose binding of the granules into composite using a biocompatible polymer.

Lee teaches improved calcium phosphate delivery vehicle or adjuvant with incorporated adjuvanticity enhancing means. The adjuvant can be fabricated to desired formulations as appropriate and based on the intended purpose. Particle sizes can be adjusted to enhance adjuvant activity. Lee also teaches that an amorphous calcium phosphate adjuvant is disclosed. A poorly crystalline apatitic calcium phosphate adjuvant is disclosed. The reference teaches that apatitic calcium phosphorous ratios of 1.3-1.75, poorly crystalline forms are believed to resorb more quickly than highly crystalline forms (page 11, lines 19+) and that the porosity of the apatite proves the desirable characteristics for immunogen (active agent) delivery to form the inventive material (page 12, lines 1+). In a preferred embodiment, the calcium-based adjuvant is combined with poly-L-lactic acid (PLLA) and/or polyglycolide (PGA) for increased

flexibility. In addition, Lee teaches PLGA, PLA, gelatin), particularly biodegradable polymers, may also increase adjuvant activity by themselves serving as a delivery vehicle for the inventive calcium phosphate adjuvant (page 20, lines 25+). Further, Lee teaches in a preferred embodiment, a calcium phosphate adjuvant is prepared as a composite of calcium phosphates with different resorption rates. Variable delivery kinetics may be achieved by combining multiple calcium phosphates having different resorption rates within one adjuvant system (page 22, lines 9+). The reference discloses that the art knew that calcium phosphates were known as tablet disintegrators; suspending agents; flocculating agents; oral detoxifying antacids and others (page 2, lines 27+).

Thus, it would have been obvious to a person having ordinary skill in the art to use poly-L-lactic acid and/or polyglycolide (PGA) to the granules disclosed by Tsuru to add adjuvanticity and /or resorbability to an oral tablet made from the granules disclosed by Tsuru.

Both references did not teach the use of soluble polymers disclosed in instant claim 9 which are entrapped in the pores with the active agent.

Isobe teaches Therapeutic/prophylactic agents for pets. The reference teaches that the formulation includes ascorbic acid and discloses that in order to mask the taste and improve the palatability, the edible organic acid or a salt thereof, especially the powdery or granular edible organic acid or a salt thereof, may be coated, and the solid preparation may be a sugar coated solid preparation (e.g. tablet) or a coated solid preparation (e.g. tablet) coated with a coating base. The examples of the coating base

include gelatin, hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, low-substituted hydroxypropylcellulose, polyethylene glycol, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, acrylic acid copolymer, carboxymethylcellulose, carboxymethylethylcellulose, and polyvinyl alcohol

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to use the polymers disclosed by Isobe for taste masking such as cellulose polymers, polyethylene glycol and polyvinyl alcohol to mask the taste and/or improve palatability of drugs such as ascorbic acid. The person of ordinary skill would be motivated to include other drugs that are known to have a unacceptable taste with the said polymers in a taste masking preparation and include it in the granules taught by Tsuru because apatites are known to have a taste masking property which is evidenced by the following references: US 20030168401 which teaches porous hydroxyapatite used in water filters to reduce containants and improve taste, US 5648399 which teaches hydroxyapatites remove salty or metallic taste, and JP 62032872 which teaches alcoholic drink taste improving agent comprises granular or porous sinter of hydroxyapatite. Therefore, the soluble polymers having taste masking properties enhance the effect of hydroxyapatite and motivate a person having ordinary skill in the art to combine both the granules teaching and the polymers teaching since both are in the same field of endeavor.

Claim 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsuru et al. EP 376331 (Tsuru) in view of Lee et al WO 0015194 and further in view of Makoto et al. “Effect of Sodium bicarbonate amount on in vitro indomethacin release

from self-setting carbonated apatite cement", Pharmaceutical Research, Vol. 14, No. 4, 1997 (hereinafter Makoto).

Tsuru and Lee are relied upon for the reasons set forth hereinabove.

Neither of the references teaches the amount of carbonate in the apatite.

Makoto studied adding sodium bicarbonate 0-10% to hydroxyapatite which resulted in increasing total pore volume of the cement matrix. Further, the reference teaches that mean drug release time and T_{50} (the time required for 50% drug release of the cement) were a function of adding the amount of sodium bicarbonate. The results of the relationship between the micropore distribution, total volume of pores after drug release and the drug release behavior supported the hypothesis that the variation in drug release from the cements resulting from the addition of sodium bicarbonate was mainly due to an increase in the diffusion of the drug in the micropores of the cement by dissolution or erosion of the cement matrix (see methods, results and conclusion).

Therefore, it would have been obvious to a person having ordinary skill in the art at the time the invention was made to use carbonated apatite having an amount of carbonate around 10% and optimize the amount of carbonate to control increasing or decreasing the pores in the apatite to the degree needed in the apatite and consequently to control the release of a drug from the granules disclosed by Tsuru using the polymers disclosed by Lee to obtained a controlled release drug that is entrapped in porous carbonated apatite.

(10) Response to Argument

Appellant argues that:

<u>Tsuru describes slow release granules of Calcium Phosphate compounds</u>

- The Tsuru reference relates to calcium phosphate compounds in general, and notes apatites, which are specific types of calcium phosphate compounds as would be appreciated by one of ordinary skill in the art. This is clearly stated on page 3, lines 15-17 of the reference noting such other compounds as tricalcium phosphates and tetracalcium phosphates to name others. Hydroxyapatite is referred to at page 5 which has a Ca/P of 1.67 which is outside of the range of 1.3 to 1.6 of claim 11 on appeal.

<u>To respond</u>: Tsuru teaches calcium phosphate compounds generically, however, the reference specifies the types of calcium phosphate used in the invention stating that the calcium phosphate compound used as a starting material of the granules is **not restricted, provided that it has a Ca/P ratio of 1.3 to 1.8. A ca/P ratio of 1.35 to 1.75 is preferable and a Ca/P ratio of 1.4 to 1.7 is more preferable**. Tsuru discloses that **typical examples** of the calcium phosphate compound useful in the invention include alpha -or beta -tricalcium phosphate, tetracalcium phosphate, **different types of apatite such as hydroxyapatite** or fluorinated apatite, and the like (page 3, lines 14-18). The reference clearly discloses hydroxyapatite having Ca/P ratio within the ranges disclosed supra. Regarding hydroxyapatite disclosed in page 5 of Tsuru which is outside of the range of 1.3 to 1.6 of instant claim 11, it is noted that the ratio of Ca/P of1.67 disclosed by Tsuru in page 5 does not exclude hydroxyapatite of the ratio of 1.3 to 1.8, 1.35 to 1.75 and ratio of 1.4 to 1.7 disclosed in page 3. It is also noted that *even if* Tsuru limits the ratio of calcium to phosphorous to 1.67 in page 5, and comparing this ratio to instant claim 11 the difference between 1.6 of instant claim 11 and 1.67 of Tsuru

is only 0.07 which is a minute difference within the purview of a person having ordinary skill in the art to optimize by doing experimental manipulations.

- The ratio of the hydroxyapatite having a ratio of 1.67 of Tsuru represents a clear teaching away from this range which is a claim limitation which cannot be ignored. Note that the claims on appeal are limited to apatites and not to the other forms of calcium phosphate referred to in the reference as would be appreciated by one of ordinary skill in the art.

To respond: Applicant alleges that Tsuru teaches away for a difference in ratio of 0.07, however, instant specification teaches ratios of calcium to phosphorous of 1.1 to 2.1 and the disclosure asserts that this range is acceptable in making the dosage form, this range includes Tsuru's ratio. It is respectfully noted that a reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. In re Gurley, 27 F.3d 551,553 (Fed. Cir. 1994). Therefore, Tsuru is not teaching away since the reference discloses ratio of Ca/P of 1.3 to 1.8 and since instant disclosure states a range of the ratio of 1.1 to 2.1 should result in the instant claimed invention.

- The oral dosages of the present invention are not suggested by the reference as noted in the sentence bridging pages 4 and 5 of the reference in the discussion of local

injection, or implantation and transvascular chemotherapy as would be appreciated by one of ordinary skill in the art.

<u>To respond</u>: though Tsuru used the granules in implantable tablets, it is noted that the intended use of the claimed composition has not been given patentable weight, because the prior art compositions would be at least capable of performing said use.

<u>Tsuru does not teach drugs within the pores of apatite</u>

- procedure described in Example 6 where the hydroxyapatite powder is coated on acryl beads (more than 50 times larger than the hydroxyapatite powder) which are then fired at 900 degrees C to form hollow granules of hydroxyapatite. There is no indication that acryl is present, because it is not, as would be appreciated by one skill in the art. Thus, one of ordinary skill in the art would appreciate that the further

<u>To respond</u>: Tsuru teaches acryl beads inside the apatite granules, Applicant argues that after heating under high temperature there is no acryl. However, Tsuru teaches a range of temperatures starting at 200°C and according to Physics laws, materials do not evanesce, and although Tsuru is silent towards the fate of the acryl beads the acryl would not vanish. Most importantly, the Office Action relies upon Isobe for teaching the polymers that help in taste masking.

- Tsuru teaches that the drug and polymers are entrapped in the pores of the apatite is not correct and is most respectfully traversed. It is the firing (sintering) which binds the hydroxyapatite powder into the porous hollow granules which is consistent with the statement in the Final Rejection that Tsuru did not disclose binding of the granules into composites using a bicompatible polymer. It is the pores between the

fused powder which retain the drug and not the pores of the apatite grains in accordance with the claimed invention. The Examiner states that Tsuru teaches that the drug and polymers are entrapped in the pores of the apatites .... This aspect of the statement is traversed. It is the granules which are impregnated with the drug not the apatite grains in accordance with the present invention.

To respond: Claim 1 in Tsuru states:

> 1. Slow, release drug delivery granules comprising porous granules of a calcium phosphate compound having a ratio of Ca to P of 1.3 to 1.8, porosity of 0.1 to 70%, specific surface area of 0.1 to 50 m2/g and pore size of 1 nm to 10 micron, calcined at a temperature of 200 to 1400°C, and a drug component **impregnated in pores of the granules.**

There is no doubt that the invention disclosed by Tsuru is porous granules where the drug is inside the pores of the granules (please see bolded text). Further, appellant alleges that the drug is in the pores between the fused powders, however, if the drugs are loaded through impregnation, it is not expected that the drug component chooses the pores between the fused powders and leaves the pores inside the granules free.

Lee does not overcome the deficiencies of the primary reference

- Adjuvant refers to any substance that is capable of producing or enhancing a host response towards a specific active agent. Hydroxyapatites are included in a group of calcium compounds But there is absolutely no teaching which suggests using a biocompatible polymer to bind the apatite grains to form a microspherical composite having a size of 0.5 -1000 microns.

To respond: primarily Tsuru discloses the use of a polymer (claim 4) such as gelatin and chitin (claim 15) and binder (claim 14), the disclosure shows that Tsuru was concerned about binding the granules. Further, Lee is relied upon to obviate the requirements of instant claim 19 and for disclosing specifically, combining calcium based adjuvant with poly-L-lactic acid (PLLA) and/or polyglycolide (PGA) for increased flexibility. In addition, Lee teaches PLGA, PLA, gelatin) to form a preferred adjuvant. It is noted that regardless of the reason of including such biodegradable polymers in Lee's invention, it is expected that the polymers should be able to perform the same function required by the instant claims since same compounds should have the same properties and perform in the same way.

- In a preferred embodiment, a liposome or polymer will encapsulate the calcium phosphate adjuvant producing microspheres. However, this is distinctly different as would be appreciated by one of ordinary skill in the art from using a biocompatible polymer to bind the grains to form a microsphere in accordance with the presently claimed invention.

To respond: as discussed hereinabove, Lee is relied upon for teaching to obviate the requirements of instant claim 19 and for disclosing specifically, combining calcium based adjuvant with poly-L-lactic acid (PLLA) and/or polyglycolide (PGA) for increased flexibility. It is noted that using a liposome or any other encapsulant may not change the fact that said polymers make a good combination with calcium based compounds which obviates the requirement of instant claim 19.

- The rejection of claims 2, 8-9 do not stand or fall with the rejection of claims 1, 3-7, 10-11, 13, -15, 18-20 and 72 as these claims contain an additional limitation that the pharmaceutical dosage form further comprises a water soluble polymer entrapped in pores of said grains which as noted on page 5 of the final rejection.

To respond: the water soluble polymers entrapped in the pores are disclosed by Isobe who teaches that such polymers help in taste masking.

- There is nothing in the reference to suggest that the water soluble polymer is entrapped in pores of the grains, but it is coated thereon. There is no suggestion of the claim limitations of the claims on appeal in this reference nor does the combination of references render the presently claimed invention obvious.

To respond: adding a polymer to an active agent is well known in the art; it is not a new process even if this mixture will be entrapped in pores. Note that Appellant claims entrapping the active agent with a polymer into pores but Appellant does not describe how the entrapping will be achieved while Tsuru is clearer in the regard choosing impregnation as a method of entrapping.

Therefore, Tsuru teaches the porous apatite granules, its size, percentage of porosity, the surface area, the pore size, the Ca/P ratio, coating the grains with gelatin or chitin and using a binder, entrapping the active agent such as antibiotics into the pores and the amount of drug loaded is inherently the same since Tsuru's pore sizes are the same. Lee teaches a preferred calcium-based adjuvant is the adjuvant combining calcium and poly-L-lactic acid (PLLA) and/or polyglycolide (PGA). Isobe is relied upon for teaching that the adding a soluble polymer such as hydroxypropylmethylcellulose,

ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, low-substituted hydroxypropylcellulose, polyethylene glycol, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, acrylic acid which are the requirements of instant claim 8. Therefore, the claims are prima fascia obvious over the combination of Tsuru, in view of Lee and further in view of Isobe.

THE SECOND OBVIOUSNESS REJECTION

- Otsuka, on page 444 under Materials and Method teaches that tetracalcium phosphate (TTCP) and dicalcium phosphate dihydrate (DCPD) and 0 - 40% (HAP) which is hydroxyapatite seed crystals with various amounts of sodium bicarbonate as summarized in table 1. The cement powder was mixed to form this cement. In the results and discussion portion on page 446, it is stated that the X-ray diffraction profiles suggest that IMC and sodium bicarbonate did not interfere with the cement setting but apatite formation was deleted by the presence of sodium bicarbonate. Note also the presence of tetracalcium phosphate.

<u>To respond:</u> Makoto (Otsuka) clearly teaches in the final CONCLUSION (page 448 bridging to page 449) that the indomethacin release rate from carbonate apatite cements increased with increasing carbonate content. The reference also teaches that the relationship between the micropore distribution, total volume of pores after drug release and drug release behavior were consistent with each other which supports the hypothesis that the variation in drug release from the cements results from the addition of sodium bicarbonate is mail due to an increase in the diffusion of the drug in the micropores.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/NABILA G EBRAHIM/

Examiner, Art Unit 1618

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/Michael G. Hartley/

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